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Evaluation Of Diagnostic Criteria In The Early Identification And Treatment Of Sepsis

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Abstract

Title: EVALUATION OF DIAGNOSTIC CRITERIA IN THE EARLY IDENTIFICATION AND TREATMENT OF SEPSIS. Christopher A. Zirker, Charles R. Wira III. Department of Emergency Medicine, Yale University, School of Medicine, New Haven, CT.

The recently introduced Sepsis-3 guidelines have yet to be applied to the emergency department (ED) setting. To compare these new definitions clinically with those of Sepsis-2, a retrospective analysis was performed using a dual-center ED registry of patients prospectively identified as having sepsis with organ dysfunction as defined by Sepsis-2. Of 446 registry patients meeting Sepsis-2 criteria, 61.0% (n = 272) had an elevated qSOFA score. 28-day in hospital mortality for patients with an elevated qSOFA was 15.8% compared to 10.9% in patients with non-elevation (p = .162). Rates of mechanical ventilation and vasopressor infusion were 38.6% and 36.4% respectively for patients with elevated qSOFA compared to 19.5% and 13.8% for patients without qSOFA elevation (p < .001). Patients with an elevated qSOFA and a serum lactate >2 mmol/L had a mortality rate of 18.1% vs 8.8% (p = .006) in patients with non-elevated qSOFA or normal lactate. Patients with septic shock as defined by Sepsis-3 (n = 50) had a mortality rate of 34.0% compared to 29.1% in patients with septic shock as defined by Sepsis-2 (n = 79; p = .565). 85.0% (n = 379) of patients had a SOFA score of 2 or higher thus meeting the definition of sepsis, with 30.5% (n = 136) of patients having all data available for calculating a complete SOFA score. Mortality rates were 15.6% in patients with a SOFA score of 2 or greater compared to 4.5% in those without (p = .016). While the Sepsis-3 definitions may help identify patients with a greater risk for mechanical ventilation, vasopressor infusion, and death, the percentage of patients meeting Sepsis-2 criteria who do not meet Sepsis-3 may limit the prognostic utility of these new definitions. Addition of serum lactate to the qSOFA may improve prognostic value and should be investigated further in the ED phase of care.

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Table of Contents

Abstract i
Acknowledgements ii
Table of Contents iii
Introduction 1
Statement of Purpose and Aims 10
Primary aims 10
Secondary aims 11
Methods 12
Study Design and Setting 12
Study Population and Measurements 13
Data Analysis 13
Results 16
Characteristics of Included Patients 16
Characteristics of Patients with Elevated qSOFA 17
Characteristics of Patients with Elevated qSOFA and Elevated Lactate 19
Performance of the Sequential Organ Failure Assessment (SOFA) Score in the ED Setting 20
Patient Outcomes 21
Discussion 23
Limitations 28
Conclusions 29
References 31
Figure References and Legends 34
Figure 1 34
Figure 2 35
Figure 3 36
Tables 37
Table 1 37
Table 2 38
Table 3 40
Table 4 42
Table 6 45
Table 7 46

Introduction

Sepsis, a common and widely recognized medical syndrome, is a heterogenous condition which carries significant morbidity and mortality. Sepsis was recently estimated to have an annual global burden of between 15 and 31.5 million cases resulting in 5.3 million deaths (1, 2). Up to nearly half of in-hospital mortality has been attributed to sepsis, and survivors experience elevated risk of rehospitalization (3, 4). Sepsis is the most expensive condition treated in US hospitals among all payers, totaling to $24 billion in 2013 alone (5). It has been estimated that sepsis costs hospitals on average around $20,000 per adult patient and between $29,829 and $65,639 per pediatric patient (4, 6). In addition to the economic burden of sepsis, there is increasing recognition of the humanistic costs for survivors including impaired quality of life, increased dependence on caregivers, and a "post-sepsis syndrome" of physical and psychological problems experienced by many sepsis survivors (4, 7, 8).

The clinical and economic burden of sepsis is undeniable, but what is sepsis? While many had written on the topic of sepsis (9-11),the first consensus definitions became available following the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, which was held in Chicago in August of 1991 (12). Prior to this meeting, the term "sepsis" was broadly recognized but lacked a well-established definition. Additionally, there were related terms such as "infection," "septicemia," "bacteremia," "septic syndrome," and "septic shock" which varied in usage and lacked standardization. The absence of clear definitions led to clinical inconsistencies and hampered coalescence of research efforts. The conference

therefore sought to develop a common definition of sepsis, standardize terminology, and establish clinical criteria which could be used for identification and improvement in management.

Subsequently, this group defined "sepsis" as "the systemic response to infection manifested by two or more of the following clinical criteria: 1) a body temperature greater than 38°C or less than 36°C; 2) a heart rate greater than 90 beats per minute; 3) tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a PaC02 of less than 32 mm Hg; and 4) an alteration in the white blood cell count, such as a count greater than 12,000/mm^3, a count less than 4,000/mm^3, or the presence of more than 10% immature neutrophils." This constellation of clinical symptoms was suggested to be a result of an inflammatory reaction to a variety of clinical insults, and was given the title "systemic inflammatory response syndrome," or "SIRS." Importantly, the title "sepsis" required the presence of infection in addition to SIRS. Conditions such as acute pancreatitis, trauma, and large burns could produce a clinical presentation which satisfied two or more SIRS criteria and therefore could be described as systemic inflammatory response syndrome, but a lack of infection would preclude these conditions from earning the title of sepsis (12).

In addition to providing working definitions for the terms "infection" and "bacteremia," several more terms were defined in recognition that sepsis had common associated sequelae. "Severe sepsis" was defined as "sepsis with associated organ dysfunction, hypoperfusion, or hypotension," where hypotension was defined as "a systolic blood pressure <90 mm Hg or a reduction of ~40 mm Hg from baseline in the

absence of other causes for hypotension." "Septic shock" was defined as "sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status." Elimination of the term "septicemia" was recommended. Lastly, this work introduced "multiple organ dysfunction syndrome," or "MODS," which was defined as the "presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention." This syndrome was described as distinct from sepsis, although it was recognized that MODS could arise within the context of SIRS. The definitions established by this group later came to be referred to in the medical literature as "Sepsis-1." (13)

One decade later, a similar group reconvened to revisit these definitions, examine their impact within the medical and research communities, and the need for ongoing revision given the availability of new data. This meeting, held in Washington, DC in December 2001, again consisted of members from the American College of Chest Physicians and the Society of Critical Care Medicine. However, these societies were now joined by members of the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society (14). This group concluded that, apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, there was no evidence to support a change to the sepsis definitions which had been introduced in 1991. However, they noted that while SIRS remained a useful diagnostic concept for sepsis, it was overly sensitive and non-specific for diagnosing the cause of sepsis or in identifying a pattern of host response (15). The organ dysfunction

present in severe sepsis could now be defined using the recently published and validated Sequential Organ Failure Assessment (SOFA) score (16, 17). The definition of septic shock was updated to recognize that children and neonates maintain greater vascular tone than adults, and therefore hypotension is a late and severe complication of an already present shock state. In place of hypotension, pediatric septic shock would be defined as tachycardia with signs of decreased perfusion such as decreased peripheral pulses compared to central, increased capillary refill time, or decreased urine output (18).

While the definitions put forth by Sepsis-1 had achieved some success in standardizing both clinical and research approaches to sepsis, the conference recognized that there did not exist a framework for precise staging of the host response to infection. The group therefore proposed a system called "predisposition, insult/infection, response, organ dysfunction," or "PIRO." As the name implies, this classification scheme sought to stratify patients based on their predisposing conditions, the nature and extent of the infection or insult, the type and magnitude of the host response, and the accompanying organ dysfunction. The group emphasized the role that a staging system such as PIRO could play in the future of treating and studying sepsis, but stated that this model itself should only act as a template upon which a full model should be built rather than as a tool to be adopted on its own. The ideas set forth by this group later came to be referred to as "Sepsis-2." (13, 14)

In January 2014, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine created a task force of 19 specialists with backgrounds

in critical care, infectious diseases, surgery, and pulmonary medicine to create "Sepsis-3." (13) Citing considerable advances in scientific understanding of the pathobiology, management, and epidemiology of sepsis since the 2001 Sepsis-2 definitions were published, this group reevaluated and updated nearly all aspects of the prior guidelines. "Sepsis" was redefined as "life-threatening organ dysfunction caused by a dysregulated host response to infection." Clinically, "organ dysfunction" was defined as an increase in the Sequential Organ Failure Assessment (SOFA) by 2 points or more. Since this new definition of sepsis required the presence or organ dysfunction, the term "severe sepsis" became superfluous and was eliminated. "Septic shock" was redefined as a subset of sepsis in which "profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone." Clinically, this was said to be identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of at least 65 mmHg and a serum lactate of greater than 2 mmol/L.

An important provision of the new Sepsis-3 definitions was the retirement of the SIRS criteria and its role as a clinical tool for the identification of patients with sepsis. The task force described the Sepsis-1 SIRS criteria as "unhelpful," and introduced a new bedside clinical score, the quickSOFA (qSOFA), to replace rather than augment SIRS. The intent of the qSOFA was to enable the rapid identification of patients who are more likely to have outcomes typical of sepsis. Recommended for use in adult patients with suspected infection outside of the intensive care unit (ICU,) the qSOFA consists of three bedside criteria: 1) systolic blood pressure less than or equal to 100 mm Hg; 2) respiratory rate greater than or equal to 22; and 3) altered mentation. When a patient

satisfies two or more of these criteria of systolic hypotension, tachypnea, and altered mentation, this “elevated” qSOFA score is intended to prompt the clinician to investigate further for organ dysfunction, the need for initiation or escalation of therapy, referral to critical care or increased frequency of monitoring, or the possible presence of infection if not previously considered.

A key feature which distinguishes the qSOFA score from the SIRS criteria which preceded it are the methods behind its development. While SIRS was created through the collective opinion of a panel of experts, the development of the qSOFA was informed by systematic literature reviews and empirical data analyses (19). Electronic health care records from 1.3 million patient encounters from 165 hospitals over 3 years were analyzed. The qSOFA was derived using data from 12 academic and community hospitals in a hospital system of southwestern Pennsylvania. This derivation cohort included all medical and surgical encounters at these facilities, including emergency department, inpatient ward and intensive care unit patients. The qSOFA was derived from this cohort by using multivariable logistic regression to analyze the clinical variables utilized by the SIRS, SOFA, and LODS scores as well as novel criteria developed according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis recommendations (20). The result of these analyses is the combination of 2 or more of hypotension, tachypnea, and altered mental status. For patient encounters occurring outside the ICU, the predictive validity for in-hospital mortality of the qSOFA score was statistically greater than both SOFA and SIRS, although SOFA outperformed both SIRS and qSOFA in the ICU setting (19).

Recognizing that serum lactate is a widely used screening tool in sepsis, the ability of serum lactate to improve predictive validity of the score was assessed in its own post hoc analyses (19). This was done using inpatient data from a 20-hospital health system in northern California, as this organization had an ongoing quality improvement program promoting frequent serum lactate measurements. The post hoc addition of lactate greater than 2.0 mmol/L to augment the qSOFA to a 4-point scale resulted in a statistically significant improvement of the AUROC from 0.79 without lactate to 0.80 with lactate, but the clinical relevance of this was deemed to be insignificant based on "numerically similar" rates of in-hospital mortality. This was tested at higher lactate thresholds with similar results.

The reception of the Sepsis-3 guidelines by the medical community was mixed. Concerns were expressed regarding the statistical methods implemented and the accompanying risk of false-positive results (21), the usage and implementation of area under the receiver operating curve to demonstrate superiority of both qSOFA and SOFA over SIRS (22), and the fundamental assumption that the SIRS criteria were unhelpful both collectively and as individual criteria (23). It was suggested that new guidelines introduce the possibility of delayed treatment by narrowing the spectrum of patients with sepsis by requiring the presence of organ dysfunction thus impeding early detection (23, 24).

An important theme of many Sepsis-3 criticisms was the choice of criteria used for the qSOFA score and the definitions of both sepsis and septic shock. The cutoff values for the individual criteria that make up the qSOFA and the exclusion of abnormal

tachycardic response have been questioned (21). Concern has been expressed that the use of only three measures in the qSOFA and two for septic shock fails to recognize other physiologic variables available to clinicians, providing fewer potential cues for providers to recognize sepsis and septic shock (25).

A significant challenge in the management of sepsis is early recognition and the initiation of appropriate care for patients, particularly at initial presentation. A limitation of the new operational definition of sepsis is the time required to collect the data required to complete the SOFA score, thus limiting its utility in triage settings. Partially in recognition of this limitation, the Sepsis-3 committee developed the qSOFA although it was accompanied with the caveat that further validation studies should be performed (13, 19). Because emergency medicine physicians were not included in the development of the Sepsis-3 consensus recommendations, the ED triage phase of care may have been suboptimally represented in the published definitions (25). Therefore, future evaluation of the qSOFA and consideration of additional bedside variables should be investigated, particularly in the ED phase of care (21, 22, 25).

Several vital sign-based criteria were suggested as useful criteria for clinicians in a triage setting for early detection of sepsis. Abnormal tachycardic response, which has been used in the SIRS criteria for more than two decades and commonly included in rapid response team (RRT) criteria, has been shown to be an independent risk factor for mortality in patients with sepsis and associated with abnormal cardiac strain (26, 27). Heart rate, together with systolic blood pressure, make up the shock index (SI; heart rate divided by blood pressure), which has been used at bedside for predicting poor

outcomes and may be useful for prognostication of patients with sepsis (28). Prior work of a Yale thesis student has shown in a population of ED patients with severe sepsis that those with sustained SI elevation have higher rates of short-term vasopressor use and a greater number of organ failures compared to those without sustained SI elevation (29).

The absence of lactate from the triage criteria and definition of sepsis is controversial (25, 30, 31). With the availability of lactate as a point-of-care test, the use of lactate at the bedside is standard of care in the emergency medicine setting. The decision tree presented in the Sepsis-3 guideline places evaluation of rapidly obtainable serum lactate after that of the SOFA score, which is traditionally a 24-hour assessment and was shown to have inferior predictive validity for in-hospital mortality outside the ICU (13, 19). Hyperlactatemia has been shown to be an independent predictor of poor outcomes in patients with sepsis, regardless of the presence of shock and additional organ dysfunction (32-35). Patients in the ED who do not clear their lactate have higher mortality and required higher rates of vasopressor support and mechanical ventilation (36). Additionally, lactate has been proposed as a biomarker of hypoxia and serial surveillance is standard of care (37).

While the SOFA itself has been prospectively validated in the ICU setting, it remains unclear if it is the best available measure of mortality and organ dysfunction versus other scoring systems such as the APACHE II, MODS, PIRO, MEDS, or SAPS II (15, 16, 38-45). While the inclusion of serum lactate into the operational definition of septic shock reflects current clinical guidelines and is supported by recent research findings, many investigators stated the need to meet stringent cutoffs for both hypotension and

hyperlactatemia to satisfy the definition of septic shock may miss patients in normotensive or alactemic shock, thus leading to delay of or failure to reach diagnosis in patients who may benefit from intervention (23-25, 46, 47). Indeed, recent work done by a prior Yale thesis student and later published has shown that there is a group of patients with sepsis who do not meet the Sepsis-3 definition of septic shock yet share elevated mortality rates (48).

The introduction of the Sepsis-3 guidelines represents an attempt to modernize the clinical definitions of a syndrome which has been the subject of a great deal of research. However, these definitions have yet to be applied to the emergency medicine phase of care. This work aims to evaluate these new criteria during the ED phase of care to inform their implementation and, if needed, suggest revisions to hone their utility during the early phase of sepsis presentations.

Statement of Purpose and Aims

The purpose of this work is to evaluate the performance of the Sepsis-3 consensus definitions for the early identification of sepsis and septic shock in the ED population. More specifically, the primary and secondary aims of this work are:

Primary aims

1. How many patients identified by Sepsis-2 bedside criteria (SIRS) can be identified by Sepsis-3 bedside criteria quickSOFA (qSOFA) in the ED phase of care?

   a. What are the differences in clinical characteristics between patients meeting qSOFA criteria versus those who do not?
   b. What differentiates patients with an elevated qSOFA from those without?

2. Are study patients with an elevated qSOFA score (≥2) at a higher risk for poor outcomes than those with a non-elevated qSOFA score (<2)?
   a. Primary outcome: 28-day mortality
   b. Secondary outcomes: need for mechanical ventilation, vasopressors during the first 72 hours of hospitalization, and blood products
3. Are there other bedside measures that enhance the qSOFA score's function?
   a. Lactate, heart rate, shock index, specific organ failures, cumulative organ failure

Secondary aims

1.) How many patients identified by Sepsis-2 bedside criteria (SIRS) can be identified by Sepsis-3 criteria using the Sequential Organ Failure Assessment (SOFA) in the ED phase of care?
   a. How many patients in the real-world setting have complete data available during the typical course of ED care for calculating a comprehensive SOFA score?
   b. What metrics are most often unavailable during the ED phase of care?

2.) Are study patients with an elevated SOFA score (≥2) at a higher risk for poor outcomes than those with a non-elevated SOFA score (<2)?

   a. Primary outcome: 28-day mortality

Methods

Study Design and Setting

This is a retrospective cross-sectional study performed using prospectively identified patients in the Yale-New Haven Hospital Emergency Medicine sepsis registry. The study was approved by the Yale Human Investigation Committee for the review of medical records by study personnel. The setting for this study is at two emergency department sites, both associated with a major academic medical center, with a total volume of more than 120,000 patient visits per year. Between July 1st, 2005 and September 5th, 2009, patients were identified in a systematic and standardized fashion by faculty members of the Section of Critical Care Medicine in the Department of Emergency Medicine. These patients were screened while in the acute care area of the Emergency Department (ED) and were identified prospectively and consecutively during pre-defined time periods. This was performed as a quality improvement initiative for tracking sepsis outcomes (e.g. short-term mortality) and quality measures (e.g. lactate measurement, time to antibiotics, implementation of early goal directed therapy) for ED patients in the Yale Health System.

Study Population and Measurements

Inclusion criteria for this study required patients be age 18 or older, meet two or more SIRS criteria, have a presumed or confirmed infection, have a lactate drawn, and have at least one newly diagnosed organ dysfunction during the current ED presentation. A complete list of inclusion and exclusion criteria are presented in Table 1. Because Sepsis-2 dictated best practice guidelines both at the time of subject identification and study design, SIRS criteria were used as a screening marker for sepsis. However, all patients included in the study meet the definition for sepsis with organ dysfunction as defined by both the Surviving Sepsis Campaign (SSC) and Sepsis-2 guidelines (13, 31). After patient enrollment, chart extraction of predetermined data points was performed by medical students and overseen by one of the investigators. All data extractors were trained in the procedure, and the techniques involved were validated by a comparison of a subset of >500 individual data points extracted in parallel by two students which demonstrated >95% concurrence of overlapping data points. These data extractors were prior medical students; this author was not involved in the process of data extraction.

Data Analysis

All data manipulation, calculations, and statistical analyses presented in this work were performed by this thesis author. For analysis of the ED phase of each patient visit, vital signs and laboratory data were those recorded closest to time of initial presentation except for respiratory rate, for which only the highest recorded value was

available. Initial serum lactate measurements were obtained either by point-of-care or central laboratory testing prior to vasopressor initiation. Patients without a serum lactate level drawn during the ED phase were excluded from the study. Vasopressor use was defined as use of any vasopressor agent at any time during the ED course for sepsis in the setting of fluid-refractory hypotension. An elevated qSOFA score was defined as a score of 2 or greater.

SOFA scores were calculated as described by Vincent et al (17). Patients without arterial blood gas data were assumed to have normal respiratory function and given a score of 0. Similarly, patients missing data for platelet count, bilirubin, or GCS scoring were assumed to lack these data due to low clinical suspicion for organ failure of these systems. Because SOFA scores are traditionally assessed over a 24-hour period, cardiovascular scores were calculated using the lowest MAP in the ED rather than the MAP at presentation. Due to a lack of data regarding the dosages of vasopressors, the type and number of vasopressors given were used as surrogate markers for cardiovascular failure. As per the SOFA definitions, only adrenergic agents were considered as vasopressors therefore inotropes such as digoxin were not counted. Patients receiving only dopamine or dobutamine were assigned a cardiovascular score of 2, epinephrine or norepinephrine and up to one other additional agent were assigned a score of 3, while patients receiving either both epinephrine and norepinephrine or one of those agents with two other agents were assigned a score of 4. Other agents included phenylephrine/neosynephrine and vasopressin. Urine output per day was not available therefore renal scores were assigned based on serum creatinine alone.

Patients with shock were categorized according to their need for vasopressors and their serum lactate level as has been previously described (48). Briefly, vasopressor-dependent patients were categorized as dysoxic shock if they have an initial serum lactate greater than 4.0 mmol/L and vasoplegic shock if lactate was 4 or less. Patients who did not require vasopressors were categorized as cryptic shock major (lactate > 4,) cryptic shock minor (lactate ≤4 and >2,) and sepsis without lactate elevation (lactate ≤2.) Sepsis-2 septic shock was defined as receiving vasopressor infusion while in the ED. Sepsis-3 septic shock was defined as receiving vasopressor infusion while in the ED and having an initial serum lactate greater than 2.

Data preparation and statistical analyses were performed using MATLAB software (R2017a; The Mathworks, Inc., Natick, MA.) All demographic, clinical, and treatment characteristics as well as outcomes among groups were evaluated using unpaired Student's t-test for continuous data or Fisher's exact test for categorical outcomes as appropriate. Continuous data is presented as mean ± standard deviation while categorical data is presented as a percentage. A one-way ANOVA was used for comparing scores between different groups of patients with varying types of shock. All statistical tests were two-tailed and the alpha value was set at 0.05 for all comparisons. The primary outcome was 28-day mortality while secondary outcomes were need for mechanical ventilation, vasopressors, and blood products.

Additional bedside criteria were added to the qSOFA score to attempt improved prognostic fidelity. Additional criteria tested were a heart rate of greater than 90 and greater than 130, shock index (heart rate divided by systolic blood pressure) of greater

than 0.8, and a lactate of greater than both 2.0 or 4.0 mmol/L. Patients with both an elevated qSOFA and an additional positive finding were compared to those who either did not have an elevated qSOFA or the additional positive finding.

Results

Characteristics of Included Patients

The registry contains a total of 521 patients although 75 patients were excluded due to lack of initial serum lactate, leaving 446 patients included in the study. The mean age was 63.7 ± 17.5 years and 50.7% were male. Of the most common infection locations, 29.8% were pulmonary, 16.1% were genitourinary, 11.2% were abdominal, and 6.3% were skin and soft tissue. The primary source of infection was unknown for 21.5% of patients. Blood cultures were sent on 95.5% of patients, urine cultures were sent on 69.1% of patients while other cultures were sent for 33.0%. 52.9% of cultures returned positive. 2.5% of patients had no cultures sent.

Per inclusion criteria, all patients had at least one new-onset organ dysfunction. The most common organ dysfunction, hyperlactatemia, was found in 54.3% of patients with a mean initial lactate level of 2.71 mmol/L. Other common organ failures were unexplained acidemia (44.6%), acute kidney injury (41.7%), transient hypotension (38.6%), hyperbilirubinemia (36.5%), decline in mental status (32.3%), hypoxemia (31.6%), elevated serum troponin (24.4%), coagulopathy (15.0%), and thrombocytopenia (15.0%). 69 patients (15.5%) had one organ failure, 114 (25.6%) had

two, 89 (20.0%) had three, 67 (15.0%) had four, while 107 patients (24.0%) had four or more organ dysfunctions. By the inclusion criteria of suspected or confirmed infection with organ failure, 367 patients (82.2%) met the Sepsis-2 criteria for severe sepsis while 79 patients (17.8%) met the Sepsis-2 definition of septic shock. 50 patients (11.2%) met the Sepsis-3 definition of septic shock.

Characteristics of Patients with Elevated qSOFA

Data displaying the classification of patients by Sepsis-3 clinical operationalization are shown in Figure 1. 272 of 446 registry patients (61.0%) had an elevated qSOFA score. Of patients with an elevated qSOFA, 227 patients (83.4%) presented with hypotension, 159 (58.5%) with altered mental status (AMS), and 236 (86.8%) with tachypnea. Of patients with a non-elevated qSOFA, 73 (42.0%) presented with hypotension, 12 (6.9%) with AMS, and 60 (34.5%) with tachypnea. 29 patients (6.5%) met no qSOFA criteria, 145 patients (32.5%) met one, 194 (43.5%) met two, while 78 patients (17.5%) met all three qSOFA criteria. Of the patients with an elevated qSOFA score, 260 (95.6%) had a SOFA score of 2 or greater, thus meeting the operational definition of sepsis. Of these 260 patients, 46 (19.5%) of these patients met the Sepesis-3 definition of septic shock based on vasopressor requirement in the ED and a serum lactate greater than 2 mmol/L. Of patients without an elevated qSOFA score, four patients met this definition of septic shock.

Data regarding source location of infection, organ dysfunction, and past medical history are shown in Table 2. There was no significant difference in age or sex between the group with non-elevated qSOFA scores versus the group with elevated scores, although 55.2% of the group with non-elevated qSOFA scores were male compared to 47.8% male with an elevated qSOFA. Patients with elevated qSOFA scores were significantly more likely to have chronic altered mental status (46.7% vs 9.8%), history of cerebrovascular accident or transient ischemic attacks (19.1% vs 10.3%), or reside in an extended care facility (36.0% vs 25.3%), and significantly less likely for their infection source to be a skin and soft tissue infection (4.4% vs 9.2%) or have non-specific immunosuppression (6.3% vs 12.6%).

Differences in SIRS criteria at presentation, initial vital signs, organ dysfunctions present, and initial laboratory values for patients based on qSOFA score are shown in Table 3. Patients with elevated qSOFA scores presented with a greater mean number of positive SIRS criteria (3.0 ± 0.8 vs 2.8 ± 0.8, $p = .016$) and were more likely to be tachypneic (89.3% vs 64.4%, $p < .001$). Elevated qSOFA scores were associated with lower systolic and diastolic blood pressures ($p < .001$), elevated shock index (1.01 ± 0.35 vs 0.92 ± 0.29, $p = .004$), and a lower GCS score (13.1 ± 3.2 vs 14.8 ± 1.1, $p < .001$). A greater mean number of organ dysfunctions were present in patients with elevated qSOFA scores (3.7 ± 2.0 vs 2.8 ± 1.6, $p < .001$), with these patients more often presenting with hypotension (43.0% vs 30.5%, $p = 0.009$), hyperlactatemia (56.6% vs 46.6%, $p = .041$), altered mental status (46.7% vs 9.8%, $p < .001$), and hypoxemia (35.3% vs 25.9%, $p = .038$). Additionally, elevated qSOFA scores were associated with higher MEDS (11.9

± 4.6 vs 10.2 ± 4.6, p < .001) and APACHE II scores (20.3 ± 7.5 vs 16.4 ± 5.5, p < .001). Patients with elevated qSOFA scores had lower platelet counts (252 ± 132 vs 279 ± 148, p = .046) and higher serum lactates (3.0 ± 2.6 vs 2.3 ± 1.5, p = .001).

Characteristics of Patients with Elevated qSOFA and Elevated Lactate

Because serum lactate is a widely used screening tool in sepsis, the characteristics of patients with an elevated lactate were studied further. The group of patients with elevated qSOFA were divided into two groups based on a serum lactate threshold of 2 mmol/L. Data are shown in Table 4. Of the 272 patients with elevated qSOFA, 158 (58.1%) had an elevated lactate while 114 (41.9%) were non-elevated. Patients with elevated qSOFA and an elevated lactate were more likely to be male (54.4% vs 38.6%, p = .010) and less likely to have a history of COPD (16.5% vs 28.1%, p = .025). No statistically significant differences were seen between sources of infection between the two groups.

Patients meeting qSOFA criteria with an elevated lactate satisfied a greater number of SIRS criteria (3.1 vs 2.8, p = .003) and were more likely to present with fever (62.0% vs 46.5%, p = .013) or tachycardia (89.2% vs 78.1%, p = .017). The group with elevated lactate had a higher heart rate (108.5 vs 100.8, p = .014) and higher shock index (1.07 vs 0.93, p = .001). Patients with an elevated lactate had a greater number of organ dysfunctions (4.34 vs 2.76, p < .001) and were more likely to present with thrombocytopenia (20.3% vs 7.0%, p = .003), hyperbilirubinemia (42.4% vs 28.1%, p =

.016), coagulopathy (21.5% vs 10.5%, p = .021), acute kidney injury (51.3% vs 32.5%, p = .003), and troponin elevation (32.3% vs 20.2%, p = .028). There was no statistical difference in serum white blood cell count, platelet count, creatinine, INR, or pH by arterial blood gas although there was a greater presence of immature neutrophils in the elevated lactate group (8.1 vs 3.4, p = .002).

Performance of the Sequential Organ Failure Assessment (SOFA) Score in the ED Setting

Availability of data required to calculate a complete SOFA score was analyzed in the real-time ED setting. The most common organ system lacking data for SOFA scoring was pulmonary, for which 269 patients (60.3%) did not have an arterial blood gas performed. The other organ systems lacking data were the liver (83 patients; 18.6%), central nervous system (9; 2.0%), and coagulation (2; 0.4%). 136 patients (30.5%) had all data available for calculating the SOFA while 258 patients (57.8%) were missing one component, 51 patients (11.4%) lacked two, and 1 patient (0.2%) lacked three.

SOFA score data is shown in Table 5. Of the 446 patients meeting study criteria, 379 (85.0%) had a SOFA score of 2 or greater. 10 patients (2.2%) had a SOFA score of 0 while 57 patients (12.8%) had a SOFA score of 1. Of the 272 patients with an elevated qSOFA score, none had a SOFA score less than 2. The mean SOFA score was significantly higher in patients who died (8.4 vs 4.6, p < .001). Mortality rates were higher in patients with a SOFA score of 2 or greater (15.6% vs 4.5%; OR 3.9, 1.9-12.9, p = .016).

Patient Outcomes

Hospital interventions and outcomes are shown in Table 6. Mean 28-day in-hospital mortality rates were 13.9% for all study patients, 32.5% (OR 6.6, 3.7-11.7, $p < .001$) for patients with vasopressor dependence within 72 hours of presentation, and 33.1% (OR 9.0, 4.9-16.6, $p < .001$) for patients who underwent mechanical ventilation. Vasopressors were given in 123 study patients (27.6%) while 139 patients (31.2%) underwent mechanical ventilation.

Patients with elevated qSOFA scores underwent greater rates of central line placement (42.6% vs 19.5%, $p < .001$), mechanical ventilation (38.6% vs 19.5%, $p < .001$), vasopressor infusion during the first 72 hours of hospitalization (36.4% vs 13.8%, $p < .001$), and administration of blood products (8.5% vs 3.4%, $p = .048$). Patients with elevated qSOFA scores tended to have higher 28-day mortality rates though this was not statistically significant (15.8% vs 10.9%, $p = .162$).

Patients with both an elevated qSOFA and a heart rate (HR) of greater than 90 did not have a higher mortality than patients with a non-elevated qSOFA or a HR less than 90 (14.8% vs 13.2%, $p = .679$). Patients with elevated qSOFA and a HR greater than 130 trended towards an increase in mortality (20.0% vs 13.3%, $p = .235$) as did elevated qSOFA with elevated shock index (17.2% vs 11.5%, $p = .097$) although neither was statistically significant.

Patients with an elevated serum lactate greater than 2 mmol/L had a mortality rate of 18.1% (OR 2.3, 1.3-4.1, $p = .006$) compared to 8.8% mortality in patients without

an elevation in lactate. Patients with both an elevated qSOFA and elevated lactate had a significantly greater mortality rate than those who did not (21.5% vs 7.9%; OR 3.2, 1.5-7.0, p = .002). Additionally, patients with an elevated qSOFA and lactate had greater rates of mechanical ventilation (46.8% vs 27.2%, p = .001), vasopressor infusion during the first 72 hours of care (44.3% vs 25.4%, p < .001), and administration of blood products (11.4% vs 4.4%, p = .047).

Mortality data for patients based on the qSOFA score and lactate level are shown in Table 7. The greatest mortality rates were seen for patients with a qSOFA of 2 and a lactate ≥ 4.0 mmol/L (36.7%, p < .001), a qSOFA of 3 and lactate ≥ 4.0 (25.0%, p = .09), and a qSOFA of 3 and lactate between 2.0 and 4.0 (23.1%, p = .24). Patients with a lactate of 4.0 or greater experienced a higher mortality rate than patients with a qSOFA of 3 (26.6% vs 19.2%).

Mortality rates by classification of shock are shown in Figure 2. As was previously reported (48), dysoxic shock carried the highest mortality rate at 50.0%, followed by vasoplegic shock (21.3%), cryptic shock major (18.5%), cryptic shock minor (12.3%), and sepsis without lactate elevation (7.2). The mortality rate of Sepsis-2 shock was 29.1% while Sepsis-3 shock was 34.0% (p = .565).

Discussion

When the Sepsis-3 task force redefined the terms which had been used to describe sepsis for more than two decades, implicit was the goal of modernizing and improving the bedside clinician's ability to recognize, prognosticate, and treat patients at risk of outcomes typical of sepsis. Sepsis-3 eliminated the SIRS criteria which had been widely used in both clinical and research settings, and introduced a new bedside score, the qSOFA, for the identification of patients at risk for outcomes consistent with sepsis. Unlike the SIRS criteria, the qSOFA was developed using data-driven techniques rather than expert opinion alone (19). The Sepsis-3 task force demonstrated better predictive validity of the qSOFA score over SIRS for suspected infection outside of the ICU but recommended additional studies be performed to further evaluate these new criteria for use in other clinical settings. For providers in the emergency department, the accurate and timely identification of patients at risk for sepsis and the ability to initiate appropriate management is key towards improving outcomes (49, 50). Analysis of implementation these new consensus recommendations in the ED setting is necessary to determine how these definitions will impact clinical care.

This retrospective study analyzed prospectively identified ED patients who met at least 2 SIRS criteria, had a suspected or confirmed infection, and were at least 18 years of age. All patients included in the registry met the Sepsis-2 definition of either severe sepsis or septic shock. Of these 446 patients, only 272 had an elevated qSOFA score of 2 or higher and, per the operationalization of Sepsis-3 clinical criteria, would not continue to be evaluated for sepsis unless the clinician already suspected the

diagnosis as shown in Figure 1. While it is expected that not all patients identified with SIRS criteria would also be identified using qSOFA, this study demonstrates that more than a third of patients identified by Sepsis-2 criteria would risk omission under the Sepsis-3 definition. A prospective trial designed to capture patients using both Sepsis-2 and Sepsis-3 criteria in the ED setting would best address whether the qSOFA can identify more sepsis patients than SIRS.

The registry patients who were identified using an elevated qSOFA score had a greater mean number of new-onset organ dysfunctions, were more likely to present with hyperlactatemia, and had greater mean serum lactates, indicating that these patients may have greater progression of illness since the degree of lactate elevation is proportional to hospital mortality (51). Since one of the qSOFA criteria is hypotension, it is not surprising that transient hypotension and low mean arterial pressure were found more often in patients with an elevated qSOFA score. The higher shock index seen with elevated qSOFA scores was driven not by an increase in heart rate but by a decrease in systolic blood pressure, as there was no difference in mean heart rate with qSOFA elevation. Similarly, altered mental status and a past medical history of CVA/TIA or chronic altered mental status were statistically more likely in patients with an elevated qSOFA, suggesting pre-existing disease is an important factor. Interestingly, patients with tachypnea as defined by qSOFA as greater than or equal to 22 breaths per minute showed a statistical increase in hypoxemia compared to patients who were tachypneic by SIRS criteria of more than 20 breaths per minute. This may be due to a higher threshold for respiratory rate being more specific for true pulmonary dysfunction, but it

could also be related to the unfortunately common clinical practice of charting a "normal" respiratory rate as approximately 20 breaths per minute.

The notion that the qSOFA score identifies a sicker group of patients is supported by a greater need for central line placement, mechanical ventilation, vasopressor use, and administration of blood products in patients with an elevated qSOFA. While 28-day mortality was not statistically greater in this population, the trend towards higher mortality and relatively low p-value ($p = 0.162$) suggests this could approach significance were the study power to be increased. The mortality of patients in this study of 15.8% for elevated qSOFA is appropriate given Sepsis-3 cites qSOFA was predictive of mortality rates greater than 10.0% (13).

Usage of the SOFA score to identify patients with sepsis resulted in 25% fewer missed cases than the use of the qSOFA score alone. While most patients were missing variables required to calculate a complete SOFA score, it outperformed the qSOFA in prognosticating patients for mortality risk. These data support further consideration of the use of the SOFA in the ED setting despite the frequent lack of complete data, although this carries the caveat that the SOFA is not a bedside score and is expected to take considerably longer to accrue sufficient data. However, the presence of additional data can only improve the utility of the SOFA as a bedside screening tool due to the cumulative nature of the organ dysfunction scoring. The assumption that an absence of data used for calculating a complete SOFA score is indicative of normal organ function is challenged by the clinical realities of incomplete and inconsistent data collection; for example, the lack of arterial blood gas data required to calculate the pulmonary

component of the SOFA score in a given patient could be due to lack of apparent clinical need due to normal respiration, or conversely due to illness severity exceeding that which allowed or would be informed by the timely collection of arterial blood. For the one in five patients who did not have bilirubin data available, it again is a weak assumption that a lack of data suggests normal organ function, as signs of liver dysfunction can be more insidious and less clinically obvious. The prognostic value of SOFA for factors such as mechanical ventilation and vasopressor support is limited since these factors themselves are incorporated directly into the scoring system.

The addition of vital-sign based clinical criteria to improve the bedside performance of the qSOFA yielded only mild prognostic value. Adding a heart rate of 90 or greater to the qSOFA score had no change in mortality. A heart rate of greater than 130 with elevated qSOFA did increase morality from 13.3% to 20%, however this was not statistically significant and only 9% of the patients in the registry met these criteria thus limiting their utility. An elevated qSOFA with elevated shock index produced a moderate increase in morality, although this was although not statistically significant and perhaps not clinically significant either.

However, the addition of serum lactate to the qSOFA score generated a statistically and clinically significant improvement in prognostication of patients at risk for poor outcomes from sepsis. Patients with elevated qSOFA and a lactate greater than 2 mmol/L consumed far greater hospital resources, as they were twice as likely to require mechanical ventilation and vasopressors during their first 72 hours of hospitalization and nearly three times as likely to require blood products compared to

patients with only an elevated qSOFA score. Furthermore, the mortality of patients with an elevated qSOFA nearly tripled from 7.9% to 21.5% in the setting of elevated lactate. In this population, the use of lactate with the qSOFA was superior to qSOFA alone for prognostication of poor outcomes.

There are several key differences between this study and the one conducted by the Sepsis-3 task force that derived the qSOFA score and found lactate to lack utility as part of the qSOFA. This study analyzed patients who were prospectively identified based on the then-current Sepsis-2 criteria, whereas Sepsis-3 defined their cohort of patients with suspected infection retrospectively through the combination of collection of body fluid cultures and administration of antibiotics within a pre-defined time period (19). While the qSOFA variables were determined from a population of patients in the ED, floors, and ICU, the cohort used for a post hoc analysis to test the utility of lactate was on a sample of inpatients only. Patients were stratified as either "ICU" or "non-ICU," thus the ED phase of care was not considered separately. These factors all complicate the validity of their conclusions of lactate data in the ED setting, as patients may present in earlier stages of illness and derive greater diagnostic benefit from the incorporation of lactate data.

Another difference between the data presented in this study and that of Sepsis-3 is the availability of GCS and lactate data. The Sepsis-3 task force made recommendations regarding the inclusion of GCS and exclusion of lactate as parts of the qSOFA bedside score to be used in the non-ICU population, although their supplemental data indicates that the vast majority of non-ICU patients did not have GCS or lactate

data available as is shown in Figure 3 (13, 19). In our study, GCS and lactate data were available in each patient, creating a possible selection bias towards sicker patients since they should generally be more likely to have a comprehensive workup. However, our mortality rates were similar to those described by Sepsis-3.

Limitations

This work has several limitations. Patient data was collected at a single health system, which limits generalizability to other settings. The number of patients included in the study is smaller than some multi-center database studies, although there is still appropriate power to generate statistically significant results (19, 52). The 75 patients who were excluded from the study because no initial lactate was drawn were found to have a mortality rate similar to those patients who had sepsis without lactate elevation, suggesting these patients were a low-risk group whose inclusion would be unlikely to alter the conclusions of the study. The process through which subjects in the registry were identified prospectively and consecutively during pre-defined time periods by a group of faculty physicians should reduce risk of selection bias, however these patients represent only a portion of the cases seen at the two ED sites during the documented time period. The use of positive SIRS criteria as a screening tool is perhaps less inclusive than the 2001 definitions, although these criteria have been widely used, are well known, and have been shown to offer reasonable sensitivity (14, 53). While conclusions can be made regarding the characteristics of patients in the sepsis registry which the qSOFA criteria does not identify, no conclusions can be made regarding the patients

who presented with sepsis which were not identified by the SIRS screening tool but would have been identified by the qSOFA. The assumption that a lack of data regarding organ function for SOFA scoring indicated a lack of clinical illness and therefore normal function is a weak assumption, as there are many reasons patients may lack data even the obvious organ dysfunction. Because data extraction was performed retrospectively, there is the risk of error due to erroneous chart information. There is also the possibility of inaccurate or biased data extraction from the chart, however a dedicated data abstraction instrument was used to minimize errors and a >95% inter-rater reliability was demonstrated between two separate investigators.

Conclusions

The Sepsis-3 definitions represent an important step forward towards developing well-defined clinical criteria for the operationalization of identifying patients with sepsis and septic shock. However, this study demonstrates that in the ED phase of care, a large percentage of patients presenting with sepsis and septic shock as defined by Sepsis-2 may not be identified by the corresponding Sepsis-3 criteria. A serum lactate greater than 2 mmol/L in addition to an elevated qSOFA score resulted in identification of patients at greater risk for mortality, vasopressor requirement, and mechanical ventilation. The SOFA score identified a greater proportion of registry patients with sepsis than did the qSOFA, although most patients lacked the data required to calculate a complete SOFA score. These data suggest that Sepsis-3 requires

further evaluation in the ED setting, and the incorporation of lactate into bedside scoring may improve prognostication of poor outcomes.

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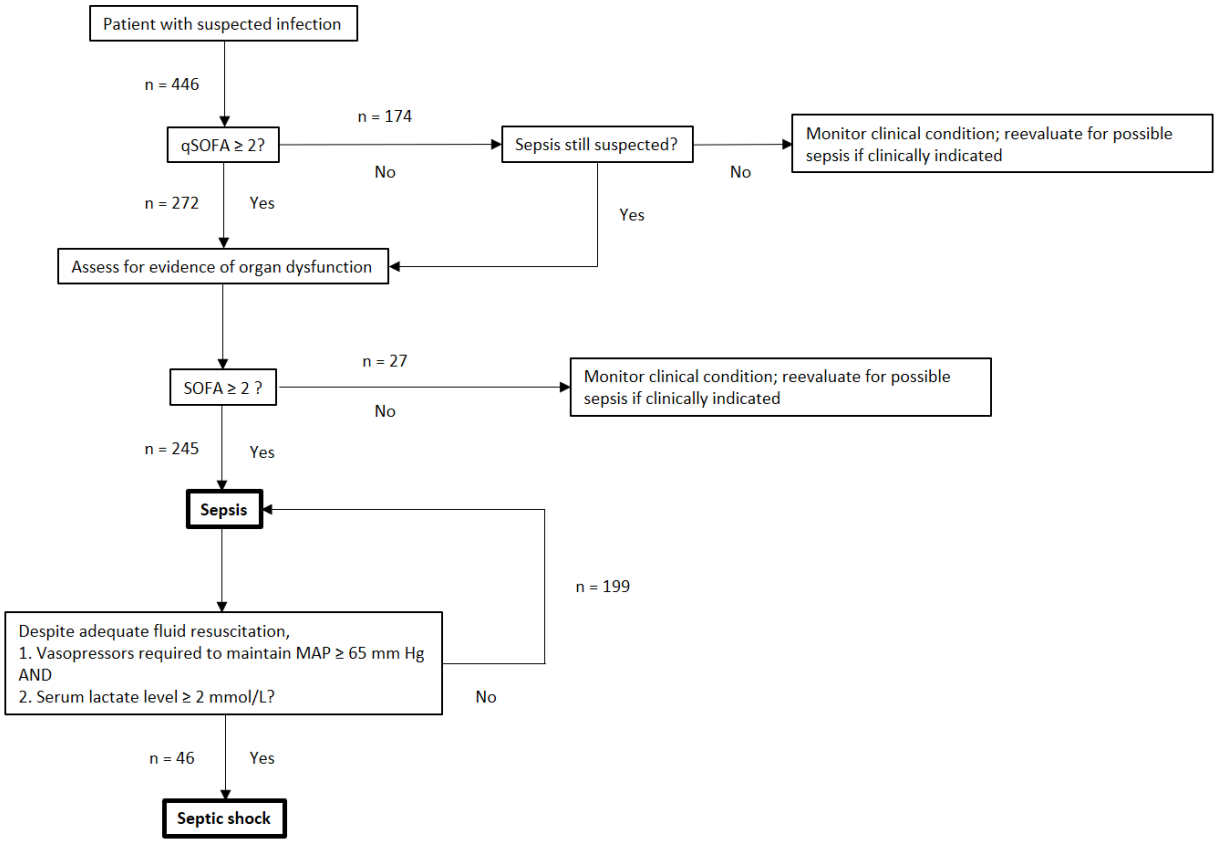
Figure References and Legends

Figure 1

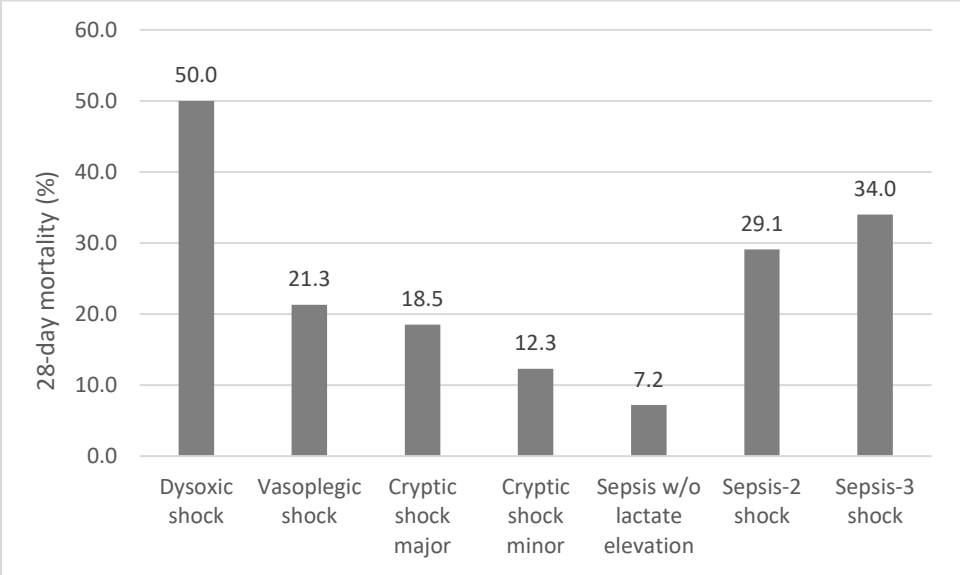
Operationalization of Sepsis-3 Criteria



Adapted from Singer et al., 2016 (13). Displays the operationalization of clinical criteria for identifying patients with sepsis and septic shock along with data from registry patients.

Figure 2

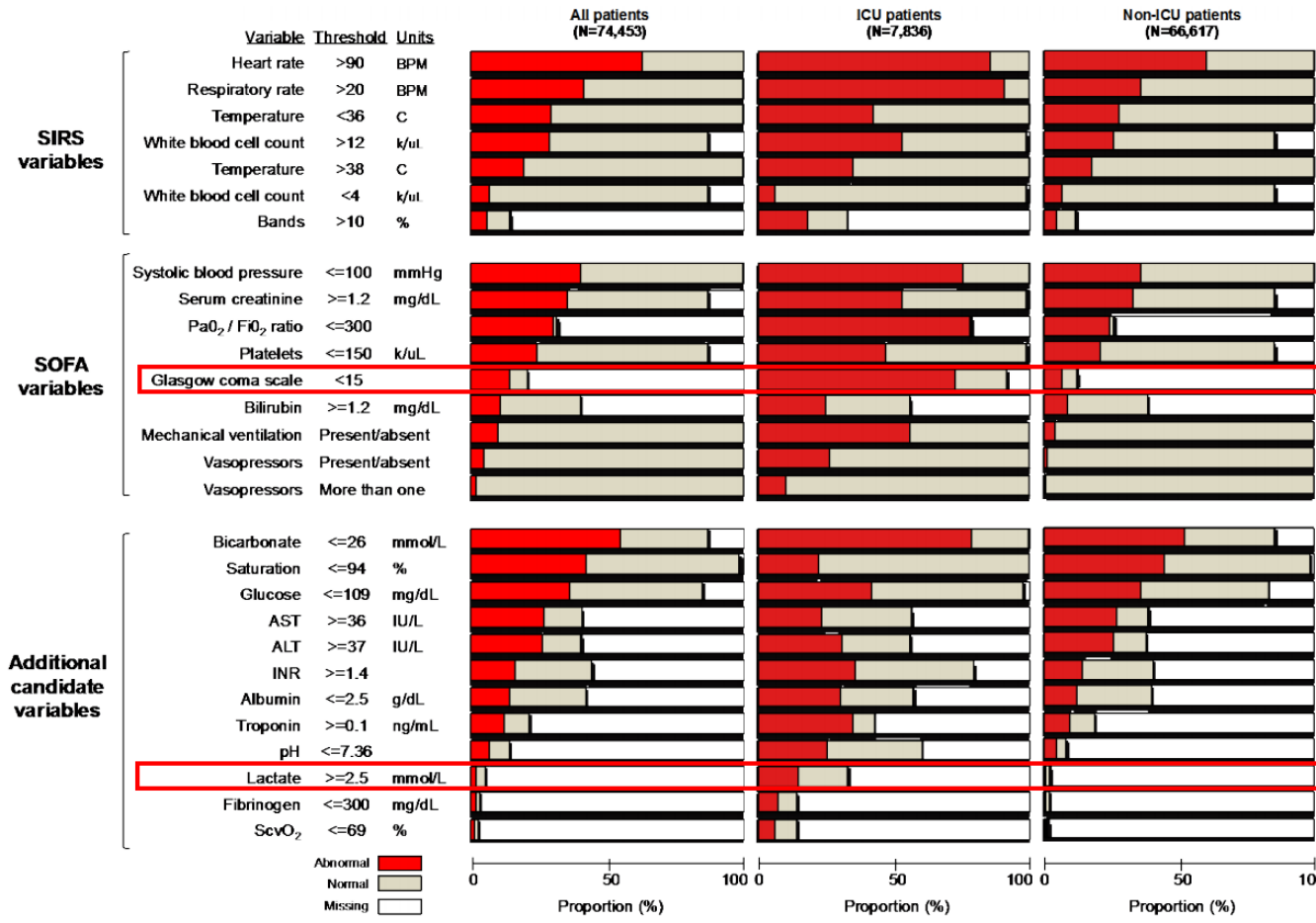
28-day mortality of patients grouped by sepsis classification



Bars are labeled with percentage of mortality rates.

Figure 3

Distribution of candidate variables used by the Sepsis-3 task force for detirming the qSOFA variables



Adapted from Seymour et al, 2016: supplemental data (19). These were variables used in the derivation cohort for determining which variables would be included in the qSOFA score. In red boxes are the Glasgow coma scale and lactate.

Tables

Table 1

Inclusion and exclusion criteria

Inclusion Criteria

1. Presumed or confirmed infection (based on documentation in ED)
2. At least 2 positive SIRS criteria during ED stay:
    a. Temperature >38.0 or <36.0 °C
    b. Heart rate >90 beats per minute
    c. Respiratory rate >20 breaths per minute or PCO_2 <32 mmHg
    d. White blood cell count >12,000 or <4,000 mm^3, or >10% immature neutrophils
3. At least one newly diagnosed organ dysfunction on admission or during patient's ED stay
    a. Transient hypotension (systolic blood pressure <90 mmHg)
    b. Hyperlactatemia (serum lactate >2.0 mmol/L)
    c. Unexplained acidemia (arterial pH <7.35 or serum bicarbonate <21 mmol/L)
    d. New neurologic dysfunction (change from baseline mental status by GCS)
    e. Thrombocytopenia (platelet count <150,000/µL)
    f. Hyperbilirubinemia (total bilirubin >1/2 mg/dL or direct bilirubin >0.2 mg/dL)
    g. Coagulation abnormalities (INR >1.10 or aPTT >30.4 without anticoagulant therapy)
    h. Acute kidney injury (creatinine >1.2 mg/dL or increase >0.5 mg/dL above baseline)
    i. Hypoxemia (O_2 saturation <90% or increase in O_2 requirement from baseline)
    j. An elevated troponin measurement (above upper limit of normal based on assay)

Exclusion Criteria

1. Patient age less than 18
2. Discharge directly from the ED
3. Documentation of a pre-existing advance directive for implementing comfort measures only
4. No lactate drawn in ED

Table 2

Baseline patient characteristics based on qSOFA scoring

	qSOFA <2 (n = 174)	qSOFA ≥2 (n = 272)
Age (years)	62.4 ± 17.7	64.5 ± 17.4
Male sex (%)	96 (55.2)	130 (47.8)
Past Medical History		
Alcohol abuse (%)	19 (10.9)	26 (9.6%)
Asthma (%)	16 (9.2)	13 (4.8)
Cancer (%)	36 (20.7)	47 (17.3)
Cancer with chemotherapy (%)	19 (10.9)	22 (8.1)
Congestive heart failure (%)	35 (20.1)	70 (25.7)
Coronary artery disease (%)	35 (20.1)	73 (26.8)
Chronic AMS[A] (%)	10 (5.7)	48 (17.6)*[H]
COPD[B] (%)	25 (14.4)	58 (21.3)
CVA[C]/TIA[D] (%)	18 (10.3)	52 (19.1)*
Diabetes mellitus (%)	59 (33.9)	89 (32.7)
End-stage renal disease (%)	18 (10.3)	34 (12.5)
HIV[E] / AIDS[F] (%)	14 (8.0)	13 (4.8)
Hypertension (%)	99 (56.9)	145 (53.3)
Immunosuppression (%)	22 (12.6)	17 (6.3)*
Liver disease (%)	17 (9.8)	22 (8.1)
Residing in ECF[G] (%)	44 (25.3)	98 (36.0)*
Documented source of infection		
Pulmonary (%)	52 (29.8)	81 (29.8)
Genitourinary (%)	22 (12.6)	50 (18.4)
Abdominal (%)	18 (10.3)	32 (11.8)
Skin/Soft Tissue (%)	16 (9.2)	12 (4.4)*
Other (%)	27 (15.5)	40 (14.7)
Unknown (%)	39 (22.4)	57 (21.0)

[A] *AMS* altered mental status
[B] *COPD* chronic obstructive pulmonary disease
[C] *CVA* cerebrovascular accident
[D] *TIA* transient ischemic attack

[E] *HIV* human immunodeficiency virus
[F] *AIDS* acquired immunodeficiency syndrome
[G] *ECF* extended care facility
[H] * denotes $p < 0.05$ between groups

Table 3

Clinical characteristics of patients based on qSOFA scores and lactate values

	qSOFA <2 (n = 174)	qSOFA ≥2 (n = 272)	qSOFA >=2 and lactate <2 (n = 114)	qSOFA >=2 and lactate >2 (n = 158)
SIRS criteria				
Number of positive SIRS[A] criteria	2.79 ± 0.75	2.96 ± 0.75*	2.81 ± 0.71	3.08 ± 0.75*[D]
Fever (%)	98 (56.3)	151 (55.5)	53 (46.5)	98 (62.0)*
Tachycardia (%)	153 (87.9)	230 (84.6)	89 (78.1)	141 (89.2)*
Tachypnea (%)	112 (64.4)	243 (89.3)*	104 (91.2)	139 (88.0)
Abnormal WBC count (%)	122 (70.1)	182 (66.9)	74 (64.9)	108 (68.4)
Initial Vital Signs				
Systolic blood pressure	120.6 ± 28.6	110.5 ± 29.3*	113.0 ± 27.5	108.7 ± 30.5
Diastolic blood pressure	69.2 ± 18.0	61.7 ± 19.3*	61.4 ± 16.4	62.0 ± 21.3
Mean arterial pressure	86.3 ± 20.1	78.0 ± 20.9*	78.6 ± 18.1	77.6 ± 22.8
Heart rate	105.0 ± 20.3	105.3 ± 25.5	100.8 ± 24.5	108.5 ± 25.8*
Shock index	0.92 ± 0.29	1.01 ± 0.35*	0.93 ± 0.29	1.07 ± 0.37*
Glasgow Coma Scale score	14.8 ± 1.1	13.1 ± 3.2*	13.2 ± 2.8	13.0 ± 3.4
Type of organ dysfunction				
Transient hypotension (%)	53 (30.5)	117 (43.0)*	52 (45.6)	65 (41.1)
Hyperlactatemia (%)	81 (46.6)	154 (56.6)*	0 (0.0)	158 (100.0)*
Acidemia (%)	71 (40.8)	128 (47.1)	49 (43.0)	79 (50.0)
Altered mental status (%)	17 (9.8)	127 (46.7)*	53 (46.5)	74 (46.8)
Thrombocytopenia (%)	27 (15.5)	40 (14.7)	8 (7.0)	32 (20.3)*
Hyperbilirubinemia (%)	64 (36.8)	99 (36.4)	32 (28.1)	67 (42.4)*
Coagulopathy (%)	21 (12.1)	46 (16.9)	12 (10.5)	34 (21.5)*
Acute kidney injury (%)	68 (39.1)	118 (43.4)	37 (32.5)	81 (51.3)*
Hypoxemia (%)	45 (25.9)	96 (35.3)*	48 (42.1)	48 (30.4)
Troponin elevation (%)	35 (20.1)	74 (27.2)	23 (20.2)	51 (32.3)*

Total number of organ dysfunctions	2.77 ± 1.56	3.68 ± 1.97*	2.76 ± 1.46	4.34 ± 2.03*
MEDS score	10.2 ± 4.6	11.9 ± 4.6*	11.8 ± 4.7	12.0 ± 4.5
APACHE II score	16.4 ± 5.5	20.3 ± 7.5*	18.3 ± 6.7	21.8 ± 7.8*
Initial laboratory values				
WBC[B] (1,000 per mm3)	14.4 ± 7.6	15.0 ± 15.7	13.7 ± 8.9	16.0 ± 19.1
Immature neutrophils (1,000 per mm^3)	5.9 ± 12.1	6.2 ± 12.2	3.39 ± 9.23	8.14 ± 9.23*
Platelets (1000 per mm^3)	278.9 ± 148.4	251.8 ± 132.4*	266.8 ± 125.7	241.2 ± 136.4
Creatinine, serum (mg/dL)	2.24 ± 2.25	2.25 ± 1.78	2.16 ± 1.86	2.31 ± 1.72
INR[C], serum	1.67 ± 2.08	1.68 ± 2.10	1.64 ± 1.64	1.71 ± 2.37
Arterial blood gas pH	7.34 ± 0.12	7.34 ± 0.14	7.33 ± 0.12	7.34 ± 0.16
Lactate, serum (mmol/L)	2.27 ± 1.48	2.99 ± 2.62*	1.22 ± 0.40	4.27 ± 2.79*

[A] *SIRS* systemic inflammatory response syndrome
[B] *WBC* white blood cell
[C] *INR* international normalized ratio
[D] * denotes $p < 0.05$ between matched groups

Table 4

Baseline patient characteristics based on qSOFA and lactate scoring

	qSOFA >=2 and lactate <2 (n = 114)	**qSOFA >=2 and lactate >2 (n = 158)**
Age (years)	63.8 ± 18.3	65.0 ± 16.7
Male sex (%)	38.6 ± 48.9	54.4 ± 50.0*[H]
Past Medical History		
Alcohol abuse (%)	9 (7.9)	17 (10.8)
Asthma (%)	7 (6.1)	6 (3.8)
Cancer (%)	21 (18.4)	26 (16.5)
Cancer with chemotherapy (%)	4 (3.5)	18 (11.4)
Congestive heart failure (%)	36 (31.6)	34 (21.5)
Coronary artery disease (%)	38 (33.3)	35 (22.2)
Chronic AMS[A] (%)	18 (15.8)	30 (19.0)
COPD[B] (%)	32 (28.1)	26 (16.5)*
CVA[C]/TIA[D] (%)	24 (21.1)	28 (17.7)
Diabetes mellitus (%)	36 (31.6	53 (33.5)
End-stage renal disease (%)	18 (15.8)	16 (10.1)
HIV[E] / AIDS[F] (%)	5 (4.4)	8 (5.1)
Hypertension (%)	63 (55.3)	82 (51.9)
Immunosuppression (%)	10 (8.8)	7 (4.4)
Liver disease (%)	7 (6.1)	15 (9.5)
Residing in ECF[G] (%)	48 (42.1)	50 (31.6)
Documented source of infection		
Pulmonary (%)	38 (33.3)	43 (27.2)
Genitourinary (%)	23 (20.2)	27 (17.1)
Abdominal (%)	8 (7.0)	24 (15.2)
Skin/Soft Tissue (%)	7 (6.1)	5 (3.2)
Other (%)	11 (9.6)	14 (8.9)
Unknown (%)	27 (23.7)	45 (28.5)

[A] *AMS* altered mental status
[B] *COPD* chronic obstructive pulmonary disease
[C] *CVA* cerebrovascular accident
[D] *TIA* transient ischemic attack
[E] *HIV* human immunodeficiency virus
[F] *AIDS* acquired immunodeficiency syndrome
[G] *ECF* extended care facility
[H] * denotes $p < 0.05$ between groups

Table 5
Differences in mortality by SOFA score

SOFA Score	# of All Patients (% of 446)	Mortality (%)	# of Patients with Elevated qSOFA (% of 272)	Mortality (%)	# of Patients with Non-Elevated qSOFA (% of 174)	Mortality (%)
0	10 (2.2)	2 (20.0)	1 (0.4)	0 (0.0)	9 (5.2)	2 (22.2)
1	57 (12.8)	1 (1.8)	26 (9.6)	0 (0.0)	31 (17.8)	1 (3.2)
2	41 (9.2)	2 (4.9)	21 (7.7)	0 (0.0)	20 (11.5)	2 (10.0)
3	50 (11.2)	2 (4.0)	17 (6.3)	0 (0.0)	33 (19.0)	2 (6.1)
4	62 (13.9)	5 (8.1)	35 (12.9)	1 (2.9)	27 (15.5)	4 (14.8)
5	57 (12.8)	5 (8.8)	35 (12.9)	4 (11.4)	22 (12.6)	1 (4.5)
6	26 (5.8)	1 (3.8)	18 (6.6)	1 (5.6)	8 (4.6)	0 (0.0)
7	43 (9.6)	5 (11.6)	34 (12.5)	4 (11.7)	9 (5.2)	1 (11.1)
8	30 (6.7)	6 (20.0)	24 (8.8)	4 (16.7)	6 (3.5)	2 (33.3)
9	19 (4.3)	6 (31.6)	17 (6.3)	6 (35.3)	2 (1.1)	0 (0.0)
10	12 (2.7)	5 (41.7)	9 (3.3)	5 (55.6)	3 (1.7)	0 (0.0)
11	14 (3.1)	10 (71.4)	11 (4.0)	7 (63.6)	3 (1.7)	3 (100.0)
12	8 (1.8)	4 (50.0)	8 (2.9)	4 (50.0)	0 (0.0)	0 (0.0)
13	10 (2.2)	2 (20.0)	9 (3.3)	1 (11.1)	1 (0.6)	1 (100.0)
14	4 (0.9)	3 (75.0)	4 (1.5)	3 (75.0)	0 (0.0)	0 (0.0)
15	1 (0.2)	1 (100.0)	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)
16	1 (0.2)	1 (100.0)	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)
17	1 (0.2)	1 (100.0)	1 (0.4)	1 (100.0)	0 (0.0)	0 (0.0)

Table 6

Hospital interventions and outcomes

	qSOFA <2 (n = 174)	**qSOFA ≥2 (n = 272)**	**qSOFA >=2 and lactate <2 (n = 114)**	**qSOFA >=2 and lactate >2 (n = 158)**
Interventions required				
Antibiotics given (%)	156 (89.7)	257 (94.5)	110 (96.5)	147 (93.0)
Central line placed (%)	34 (19.5)	116 (42.6)*[A]	47 (41.2)	69 (43.7)
Mechanical ventilation (%)	34 (19.5)	105 (38.6)*	31 (27.2)	74 (46.8)*
<72 hour vasopressor use (%)	24 (13.8)	99 (36.4)*	18 (15.8)	46 (29.1)*
Blood products given (%)	6 (3.4)	23 (8.5)*	5 (4.4)	18 (11.4)*
Mortality				
28-day mortality (%)	19 (10.9)	43 (15.8)	9 (7.9)	34 (21.5)*

[A] * denotes $p < 0.05$ between groups

Table 7

Mortality per qSOFA and Serum Lactate Values

		Lactate Threshold (mmol/L)			
	Deaths/Group (%)	**≤2**	**2.0 to 4.0**	**≥4.0**	**All Lactate**
qSOFA	**0**	0/10 (0)	0/16 (0)	0/3 (0)	0/29 (0)
	1	9/80 (14.5)	7/47 (14.9)	3/18 (13.8)	19/145 (13.1)
	2	7/90 (15.4)	10/74 (13.5)	11/30 (36.7)*[A]	28/194 (14.4)
	3	2/24 (14.2)	6/26 (23.1)	7/28 (25.0)	15/78 (19.2)
All qSOFA		18/204 (8.8)	23/163 (14.1)	21/79 (26.6)*	

[A] * denotes increased mortality with $p < 0.05$ between group meeting given lactate and qSOFA criteria and all remaining study patient not meeting given criteria